

REVIEW ARTICLE

Age at menarche and risk of asthma: systematic review and meta-analysisSofie Lieberoth, BSc.med¹, Elisabeth Juul Gade, MD¹, Jesper Brok, MD, PhD², Vibeke Backer, MD, DMSc¹, and Simon Francis Thomsen, MD, PhD³¹Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen, Denmark, ²Department of Pediatrics, Rigshospitalet, Copenhagen, Denmark, and ³Department of Biomedical Sciences, Center for Medical Research Methodology, University of Copenhagen, Copenhagen, Denmark**Abstract**

Background: Several studies have suggested a relationship between the age at menarche and risk of asthma development. **Objective:** To conduct a systematic review and meta-analysis of the relationship between the age at menarche and the risk of asthma. **Methods:** This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). A pre specified literature search strategy was used to identify studies of potential relevance and independent reviews were carried out by two authors. Raw data was pooled using the software package RevMan to calculate summary odds ratios. The risk of publication bias was assessed graphically by using a funnel plot and the robustness of the overall estimate obtained was assessed by using sensitivity analyses. **Results:** The searches identified 61 potentially relevant articles of which seven articles, with a total of 22 859 subjects, matched the inclusion criteria for the meta-analysis. Pooling of the seven studies showed that girls with early menarche (<12 years) had an increased risk of asthma relative to girls with late menarche; random effects odds ratio = 1.37 (1.15–1.64), ($p = 0.0005$). Substantial heterogeneity was revealed ($I^2 = 55\%$). Sensitivity analysis showed that the risk estimate was not markedly changed when excluding any of the studies. The funnel plot did not indicate publication bias. **Conclusions:** Early menarche appears to be associated with increased risk of asthma. Hormonal, immunological, genetic and environmental factors may act in a developmental context to explain this relationship. Future studies are warranted to further determine the mechanisms responsible for this observation.

Keywords

Asthma, epidemiology, Menarche, Meta-analysis, Systematic review

History

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Introduction

The prevalence of asthma has increased substantially during the last decades [1]. This increase is likely to have been caused by recent changes in lifestyle and environmental factors, but the causes are not yet fully understood. Age at menarche has been a factor of interest as recent studies have suggested a link between early age at menarche and risk of asthma [2–10]. It is well known that asthma is more prevalent among boys before puberty, but becomes more prevalent among girls after puberty [11–15]. This trend has been suggested to be due to the levels of female sex hormones that increase during puberty. In consistence with this, other studies have shown that both endogenous and exogenous female sex hormones can modulate pulmonary inflammatory processes and smooth muscle function, and thereby play a role in the

occurrence of asthma in women [16,17]. To our knowledge, no previous meta-analysis on the subject has been performed. Consequently, we conducted a systematic review and meta-analysis of the relationship between the age at menarche and risk of asthma.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [18]. If possible data were collected from studies matching the inclusion criteria for the meta-analyses, otherwise, data were requested from the authors.

Literature search

For our literature search we used a clearly defined search strategy including both MeSH terms and text search. We applied MEDLINE/PubMed, EMBASE, Cochrane Library and ISI Web of Science and searched for “asthma AND menarche”, “wheeze AND menarche” and “bronchial hyper reactivity AND menarche” until 1 March 2014. There were no restrictions in terms of language or year of publication.

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Study selection

All articles identified by the searches were independently scrutinized based on their abstracts and titles. Two authors independently reviewed titles of all citations obtained from the search and extracted pre-defined data regarding year of study, study design, bias risk, characteristics of participants and outcome measures. In case of disagreement, consensus was reached through discussion. Studies not matching the inclusion criteria were excluded from the meta-analysis, but considered for the systematic review.

Study quality

All studies included in the meta-analysis were quality-assessed to identify studies of poor quality for potential bias. Study quality and risk of bias was assessed through a quality assessment process based on the quality assessment model created by Angelillo et al. and presented by La Torre et al. [19]. Articles were given up to a maximum of 14.5 possible points for least risk of bias. Studies of poor quality defined as a quality score below seven were excluded.

Inclusion criteria for the meta-analysis

Definition of early menarche

Menarche at 12 years of age or younger.

Definition of asthma

Post-menarchal asthma, defined as asthma, either by self-report of asthma or self-report of diagnosed asthma. Only asthma defined as a categorical variable (yes/no to asthma) would be accepted.

Data

Studies presenting results suitable for pooling, i.e. fitting in a 2×2 table. Only, raw unadjusted numbers of girls with early (≤ 12 years) or late (> 12 years) menarche who either did or did not develop asthma were considered eligible. Longitudinal data on menarche and asthma were accepted, but would be recalculated into categorical data by division into the groups: ever or never asthma and early (≤ 12 years) or late (> 12 years) menarche.

Participants

Females, followed at least until age 16 with complete data on asthma and age at menarche. Only subjects with no history of asthma before menarche (post-menarchal asthma) were considered eligible.

Types of studies

Prospective and retrospective cohort studies and cross-sectional studies with or without adjustment for confounders.

Studies excluded from the meta-analysis, but included in the systematic review

Studies on age at menarche and risk of asthma not suitable for pooling, but with risk estimates for asthma in girls with early menarche, were excluded from the meta-analysis, but

considered for the concise review. These would be studies on pre-menarchal asthma, asthma symptoms such as BHR (bronchial hyper reactivity) or asthma attributes such as severity and studies not following girls until age 16 or older (e.g. for long enough for post-menarchal asthma to occur).

Statistical methods

Data were pooled using the software package RevMan [20] to calculate summary odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Two times, two tables were computed based on the raw data from the articles. In studies, early age at menarche had not been defined clearly, menarche before the age of 12 years was chosen as a cut-off. To investigate both clinical and statistical heterogeneity, the I^2 statistic was used. Furthermore, we calculated the Tau-squared statistic (between-study variance). We assumed considerable heterogeneity due to the broad inclusion criteria and consequently random-effects modelling was used to undertake the meta-analysis. The risk of publication bias was assessed graphically by a funnel plot [21] and the robustness of the overall estimates obtained was assessed by sensitivity analyses. For sensitivity analyses the software program Comprehensive Meta-Analysis, Version 2 [22] was used. The sensitivity analyses was conducted by performing both fixed and random effects analyses and by excluding the studies one at the time to see if there was a (identify any) significant change in the results.

Results

Our searches identified 61 potentially relevant studies. Of these, 13 studies with data on age at menarche AND asthma OR wheeze OR bronchial hyper reactivity were identified by our searches [3–10,23–27]. Of these 13 studies, seven were included in the meta-analysis [5–10,27] (Figure 1).

Results of the meta-analysis

The seven studies included in the meta-analysis are detailed in Table 1. No studies were excluded on the basis of poor quality defined as a quality score below seven. All studies included in the meta-analysis were cohort studies and comprised between 768 and 6944 study subjects. The cumulative number of study subjects included in the meta-analysis was 22 859. Studies were carried out in Europe or in the US and published between 2000 and 2013. All analysed studies were based on questionnaires and defined asthma as either self-report of asthma, diagnosed asthma or asthma symptoms.

Results of the meta-analysis are listed in Figure 2. Pooling of the seven studies eligible for our meta-analysis showed that girls with early menarche had an increased risk of asthma relative to girls with late menarche: random effects OR = 1.37 (1.15–1.64), $p = 0.0005$. Substantial heterogeneity was revealed ($I^2 = 55\%$). The between-study variance (tau-squared) was 0.03. Fixed effects meta-analysis also showed an increased risk of asthma in girls with early menarche: OR = 1.30 (1.18–1.43), $p < 0.0001$. The sensitivity analysis showed that the risk was not markedly changed when excluding any of the studies (Figure 3). The funnel plot did not indicate publication bias or other types of bias (Figure 4).

Figure 1. PRISMA flow diagram.

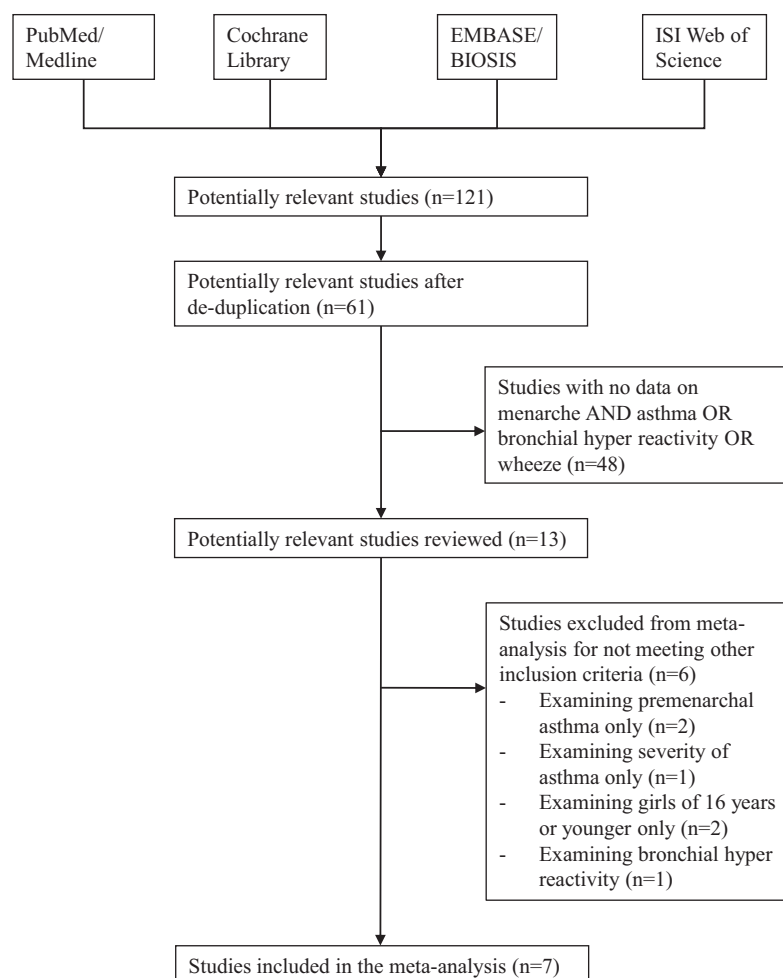


Table 1. Characteristics of the studies included in the meta-analysis.

Study	Design	Population age	Population size	Definition of early menarche	Age at follow-up	Definition of asthma	Quality assessment
1) Xu [5]	Retrospective cohort study	Pregnant mothers	5188 mother/daughter pairs	<11 years	31 years	Self-reported asthma	8.5
2) Herrera-Trujillo [6]	Retrospective cohort study	11–24 years	6994	≤11 years	11–24 years	Self-reported asthma symptoms	12
3) Salam [7]	Prospective cohort study	School age at baseline	905	≤12 years	13–28 years	Self-reported diagnosed asthma	10
4) Macsali [8]	Retrospective cohort study	27–57 years	3354	≤10 years	27–57 years	Self-reported asthma symptoms	8
5) Al-Sahab [9]	Prospective cohort study	8–11 years at baseline	1176	<11.56 years	18–21 years	Self-reported diagnosed asthma	10
6) Fida [10]	Retrospective cohort study	>18 years	3461	<12 years	>18 years	Self-reported diagnosed asthma	10
7) Gnatiuc [27]	Prospective cohort study	7 years at baseline	1968	<12 years	33 years	Self-reported asthma	10

Quality assessment based on a model created by Angelillo et al. as presented by La Torre et al. [19]. Articles are given points up to a maximum of 14.5 possible points (least risk of bias).

Studies on post-menarchal asthma, included in the meta-analysis

Characteristics for the seven studies included in the metaanalysis [5–10,27] are listed in Table 1. All included studies were based on mainly Caucasian or Hispanic populations. The study by Herrera-Trujillo et al. [6]

demonstrated that obese girls with early menarche had a significantly higher risk of asthma than those with late menarche. Salam et al. [7], Macsali et al. [8] and Gnatiuc et al. [27] reported that girls with early menarche had a higher risk of asthma irrespective of adjustment for BMI and other covariates. Al-Sahab et al. [9] and

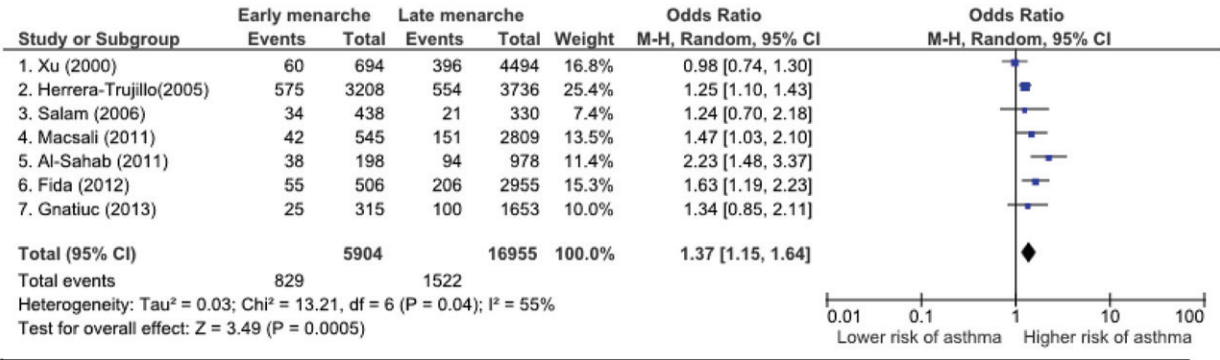


Figure 2. Forrest plot.

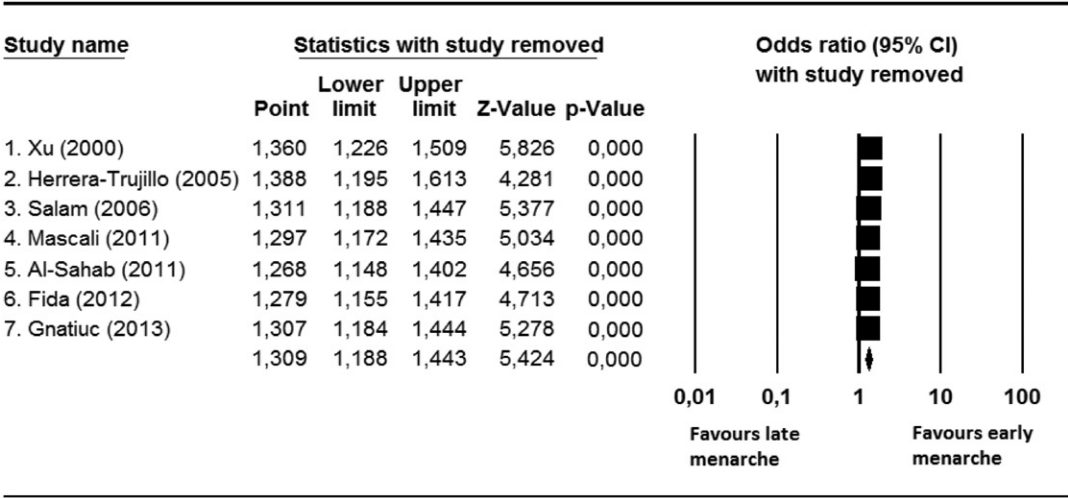
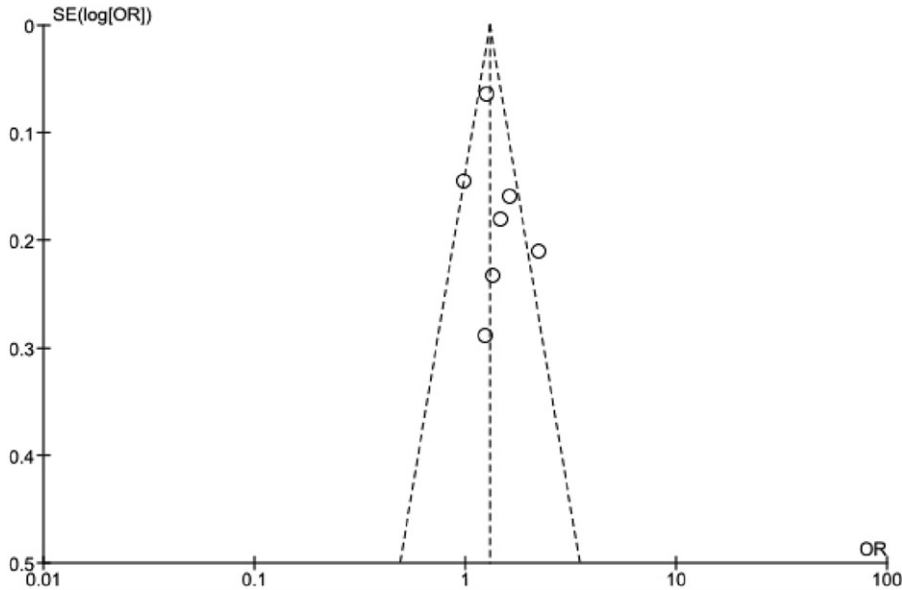


Figure 3. Sensitivity analysis.

Figure 4. Funnel plot.



Fida et al. [10] showed that early menarche was associated with a higher risk of asthma, adjusting for some covariates not including BMI. The study by Xu et al. [5] did not investigate the association between early menarche and risk of asthma,

however data for such analysis were available in the paper. When calculating odds ratios from Xu et al.'s data, we found no significant association between age at menarche and risk of asthma.

Studies on post-menarchal asthma, not included in the meta-analysis

Both studies on post-menarchal asthma excluded from the meta-analysis [3,4] addressed the association between obesity and asthma. The first study, by Castro-Rodriguez et al. [3], reported a higher prevalence of asthma symptoms among obese girls, exclusively occurring in girls with early menarche (<11 years). Varraso et al. [4] supplemented these findings, with data on asthma severity, finding a stronger association between obesity and asthma severity in girls with early menarche. Study characteristics are listed in Table 2.

Studies addressing pre-menarchal asthma and/or asthma related symptoms

The four studies excluded from the meta-analysis for addressing pre-menarchal asthma or asthma symptoms presented conflicting results [23–26]. Drosdzol et al. [24] found an association between pre-menarchal asthma and risk of early menarche, however Skrzypulec et al. [25] found the opposite association. Subsequently, Nicolai et al. [26] found that attaining menarche earlier could be associated with loss of pre-menarchal asthma, but the opposite for BHR. However, Dratva et al. [23] found that girls with BHR had a lower mean age at menarche than girls with no BHR. Study characteristics are listed in Table 2.

Discussion

This meta-analysis found a 37% increased risk of asthma in girls with early menarche when pooling seven recently published population studies with a substantial number of

study subjects; 22 859. Sensitivity analysis showed that the pooled OR was not markedly changed when excluding any of the studies, suggesting that our findings were not based on any study alone. Thus our meta-analysis appears to be robust.

Framing of the study

This study did not include studies on pre-menarchal asthma in the meta-analysis, as post-menarchal and pre-menarchal asthma naturally cannot be pooled. A separate meta-analysis of pre-menarchal asthma was not performed, as data on this subject was too sparse [24–25].

We chose not to include studies on asthma attributes, such as severity, as such data cannot be pooled with our binary data on asthma. The search was extended to BHR and wheeze, as these outcomes are sometimes used as diagnostic surrogates for asthma in the literature and thus might contribute with valuable information in the review. However, we did not include these in the meta-analysis, as wheeze and BHR do not occur in all asthma patients and thus doing so would introduce major bias.

In this study participants had to be followed at least until age 16. To our knowledge, the literature does not currently provide a definition of time to post-menarchal asthma and when to make a relevant cut-off. In choosing this cut off, we prioritized to include as many girls as possible who had attained menarche, while loosing as few cases of post-menarchal asthma as possible. In lack of a clear definition of early menarche in the literature, we chose 12 years or younger as cut-off point for early menarche. Data from the only study using continuous data on menarche [8] suggest that 12 years of age seems a relevant cut-off point for early menarche.

Table 2. Characteristics of the studies not included in the meta-analysis.

Study (publication year)	Design	Population size	Age at baseline	Age at follow-up	Definition of early menarche	Conclusion/Results	Reason for exclusion from meta-analysis
Castro-Rodriguez [3] (2001)	Prospective	1246	6	13	<11	Stronger association between obesity and asthma in girls with early menarche	Follow-up at age 13
Nicolai [26] (2001)	Prospective	234	9–11	11–14	None	At age 14, girls who attained menarche more often had lost symptoms, compared to girls who did not attain menarche (70.4 versus 62.5%)	Follow-up at age 14 and premenar-chal asthma symptoms as exposure.
Varraso [4] (2005)	Case-control	221 cases 155 controls	>16	>16	≤11	Stronger association between BMI and asthma in women with early menarche ($r = 0.20$, $p = 0.03$)	Asthma severity as outcome
Drosdzol [24] (2007)	Case-control	111 cases 53 controls	8–17	8 –17	None	Lower age at menarche in asthmatics compared to controls (10.8 versus 12.2)	Premenarchal asthma as exposure
Skrzypulec [25] (2007)	Case-control	50 cases 30 controls	12–19	12–19	None	Higher age at menarche in asthmatics compared to controls (12.3 versus 11.9)	Premenarchal asthma as exposure
Dratva [23] (2010)	Retrospective	704	18–60	18–60	None	Significantly lower age at menarche in girls with BHR (13.4 versus 13.8, $p = 0.04$)	BHR as outcome

Asthma is a complex disease and is likely to include different phenotypes, which may have different etiological factors, but we were unable to do separate meta-analyses of asthma phenotypes, as data suitable for such analyses are not yet available.

Findings of the meta-analysis and systematic review

The main finding of our meta-analysis was a significantly higher risk of asthma in girls with early age at menarche. We found a 37% increased risk of asthma, which is comparable to the fraction of liability of asthma explained by most known genetic and environmental risk factors. However from a clinical standpoint it is not overwhelming.

The seven studies included in the meta-analysis presented quite consistent results, as six out of seven studies found an increased risk of asthma in girls with early menarche, the exception being the seventh study only showing a weak tendency of the opposite, e.g. a lower risk of asthma in girls with early menarche. The study on menarche and BHR, included in the review, but not in the meta-analysis, suggested a higher risk of BHR in girls with late menarche relative to girls with early menarche [23]. This finding was unexpected, as BHR is an intermediate trait underlying asthma, and may be explained by a heavier representation of patients with BHR and no asthma in the late menarche group.

The association between early menarche and risk of asthma

Early menarche and asthma risk in women has previously been thoroughly reviewed and several risk factors for both asthma and early menarche have been identified [29,30]. In spite of this, the mechanisms in the association are not fully understood.

As asthma is more prevalent among boys before puberty, but becomes more prevalent among girls after puberty [11–15], it has been speculated that sex hormones may explain the relationship. In line with this, sex hormones can modulate pulmonary inflammatory processes and smooth muscle function, and thereby play a role in the occurrence of asthma in women [17,28]. Further, asthma has been associated with many sex hormone-related factors such as oral contraceptive use, polycystic ovarian syndrome, pregnancy, irregular menstruations and menopause and hence the incidence of asthma [29,30]. However, sex hormones alone probably cannot fully explain the association, as sex hormones vary according to the underlying metabolic condition, insulin sensitivity, body fat mass and degree of physical activity [30].

Along with sex hormones, obesity has been given much attention. As obesity is associated both with asthma, early menarche and higher levels of female sex hormones, it has been speculated that obesity could cause all three occurrences and thus explain the association. This theory naturally raises the question if there is a higher risk of asthma among women with early menarche irrespective of BMI, or only among those who are obese. Our review included three studies that reported a more evident association between obesity and asthma in women with early menarche [3,4,6], and two studies that reported the association between post-menarchal asthma

and age at menarche to be significant even when adjusting for BMI [6,7]. These studies suggest that obesity alone probably does not explain the association between early menarche and risk of asthma.

Recent evidence suggests that other factors, as well as obesity, influence the relationship between age at menarche and risk of asthma [30]. Factors such as heredity, metabolic factors, diet, physical activity, early rearing environment and intrauterine environment reflected in low birth weight, along with several unknown factors that are probably involved [30].

How these factors interact and affect age at menarche and asthma is not fully understood. Therefore, more studies investigating different aspects of the association are warranted.

Strengths and limitations

Age at menarche is an important event in a woman's life and recall bias appears to be small [31]. Nevertheless, it must be acknowledged that recall bias cannot be excluded, especially in studies with long follow-up, as bias from recall of menarche timing may be higher in long recalls. The included studies had no objective verification of disease status, which could have made the asthma diagnosis more reliable. Self-report of asthma may have given rise to bias from individual interpretation of diagnosis, especially recall regarding asthma in childhood may have given rise to an overestimation of new-onset asthma after menarche (post-menarchal asthma). On the other hand, self-reported asthma has proven to reflect physician diagnosis accurately [32,33] and not to risk rejection of potentially relevant and important findings. This meta-analysis comprised both retrospective and prospective cohort studies. Ideally, these study types should not be pooled, but the bias arising from this is small, especially compared to the benefits of a broad search. The heterogeneity was substantial ($I^2 = 55\%$), but could have been higher. We suspect that not mixing retrospective and prospective studies and using studies from populations of more similar demographics would have heightened the heterogeneity. Also the number of studies included was only seven, and thus in-between study variance could be hard to estimate. Finally, we used raw unadjusted data and thus our finding of a 37% increased risk of asthma is unadjusted and lacked adjustments in order to estimate the actual risk accurately.

The main strength of this study is the broad search strategy employed and the thorough quality assessment of potentially eligible and omitted studies. Furthermore, we extended our inclusion criteria to include epidemiological studies and all studies with data on age at menarche and post-menarchal asthma.

Previous reviews [28–30,34,35] have addressed the relationship between hormones, adiposity and asthma, but to our knowledge this meta-analysis is the first to address the association between age at menarche and the risk of asthma.

Conclusion

In conclusion, current epidemiological evidence suggests that early menarche is associated with a higher risk of developing postmenarchal asthma. Our meta-analysis supports this observation, documenting an increased risk of 37% of

postmenarchal asthma in girls with early menarche. A direct clinical consequence of this study should be a greater awareness of the relationship between early menarche and risk of asthma both in hospital settings as well as in primary care.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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